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PRINCIPAL INVESTIGATOR: Steven A. Narod, M.D.

CONTRACTING ORGANIZATION: The Centre for Research in Women's Health
Toronoto, Ontario M5G 1N8 Canada

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Steven A. Narod, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Centre for Research in Women's Health
Toronoto, Ontario M5G 1N8 Canada

E-MAIL:
narod@ftn.net

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Two genes for hereditary breast cancer, BRCA1 and BRCA2, have now been identified (Miki et al, 1994, Wooster et al, 1995). The lifetime risk for breast cancer exceeds 80% in carriers of mutations in either of these genes (Ford et al, 1994). It is now possible to identify families with mutations in these two genes and genetic testing is underway in laboratories of the principal investigator and the co-investigator.

The risk of second primary breast cancer in women with BRCA2 or BRCA2 mutations is high. Up to 60% of carriers will develop a contralateral cancer if they survive the initial cancer (Ford et al, 1994). Because of this very high risk, some women opt for prophylactic mastectomy. Other women are requesting either unilateral or bilateral mastectomy at the time of diagnosis in the hope that this will diminish their risk for subsequent cancers. There is no information yet on how these different treatments impact upon patient survival. Our objective is to establish whether women with hereditary breast cancer benefit from more extensive surgery than simple lumpectomy.

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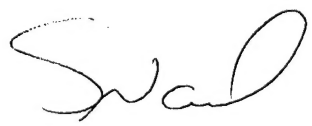

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INTRODUCTION

Two genes for hereditary breast cancer, BRCA1 and BRCA2, have now been identified (Miki et al, 1994, Wooster et al, 1995). The lifetime risk for breast cancer exceeds 80% in carriers of mutations in either of these genes (Ford et al, 1994). It is now possible to identify families with mutations in these two genes and genetic testing is underway in the laboratories of the principal investigator and the co-investigator.

The risk of second primary breast cancer in women with BRCA1 or BRCA2 mutations is high. Up to 60% of carriers will develop a contralateral cancer if they survive the initial cancer (Ford et al, 1994). Because of this very high risk, some women opt for prophylactic mastectomy. Other women are requesting either unilateral or bilateral mastectomy at the time of diagnosis in the hope that this will diminish their risk for subsequent cancers. There is no information yet on how these different treatments impact upon patient survival. Our objective is to establish whether women with hereditary breast cancer benefit from more extensive surgery than simple lumpectomy.

Tamoxifen use has been associated with a 39% reduction in contralateral breast cancer (Early Breast Cancer Trialists Collaborative Group). Because of the high risk of contralateral breast cancer in BRCA1 and BRCA2 carriers, it is of interest to establish if this drug is useful in reducing second primary breast cancers in this subgroup. Furthermore, if the rates of contralateral breast cancer are reduced substantially, there will be compelling reasons to believe that tamoxifen has potential as a chemopreventive agent in healthy gene carriers.

Similarly, ovarian ablation was associated with a 26% reduction in mortality from breast cancer in women under 50 with stage 1 or stage 2 disease (Early Breast Cancer Trialists Collaborative Group). From our early experience, 40% of women with breast cancer and BRCA1 mutations undergo oophorectomy at or near the time of mastectomy, primarily as a preventive measure against ovarian cancer. This provides us with the opportunity to ask whether or oophorectomy influences overall mortality from breast cancer and whether it reduces the incidence of contralateral tumours.

Our objective is to establish whether women with hereditary breast cancer benefit from more extensive surgery than simple lumpectomy.

BODY

Hypothesis:

Our main hypothesis is that mastectomy will be associated with a greater survival than lumpectomy in women diagnosed with stage I or stage II breast cancer, and who carry a BRCA1 or BRCA2 mutation. Our subhypotheses are: 1) treatment with tamoxifen reduces the risk of death from cancer and of contralateral breast cancer in this subgroup, and 2) that oophorectomy reduces the risk of death from cancer and of contralateral breast cancer in this subgroup.

Technical Objectives:

1) To identify 500 women, living or deceased, diagnosed with stage I or stage II breast cancer, from 1975 to the present, at age 65 or below, and who belong to a family documented to carry a BRCA1 or a BRCA2 mutation.

2) To review the medical record of these 500 women and to document the initial presentation and treatment of the breast cancer, including tumour size, stage, grade, the surgical procedure performed, the use of adjuvant chemotherapy, radiotherapy, tamoxifen, and oophorectomy.

3) To obtain follow-up information on these women, including age and cause of death, age of local recurrence, if any, and age of contralateral breast cancer, if any.

4) To perform a survival analysis on this historical cohort using a proportional hazards model, adjusting for size, stage and grade of tumor, number of nodes involved, the age of diagnosis and the estrogen and progesterone receptor status. The principal predictive variable of interest will be lumpectomy versus mastectomy (unilateral and bilateral). Additional variables of interest will be the use of tamoxifen (ever/never use and duration of use) and a history of bilateral oophorectomy (yes/no; date). We will calculate relative risks for survival based on the type of surgery, adjusting for the other predictive variables.

Statement of Work:

Task 1. Years 1-3:
We will to identify 500 women with breast cancer from a family for which a BRCA1 or a BRCA2 mutation has been identified during the three year period of this study. These women will be living or deceased, will have been diagnosed with stage I or II breast cancer in 1975 or thereafter, at the age of 65 or below.

Task 2. Years 1-3:
We will review the medical histories of these women and obtain information relating to surgical and medical treatment of the first breast cancer. We agree to obtain follow-up information on these women regarding the date and cause of death, breast cancer recurrence in the same and opposite breast.

Task 3. Years 2-3:
We will perform a statistical analysis on this data set in order to estimate the protective effect of mastectomy vs oophorectomy in this cohort, and evaluate whether there is any protection associated with tamoxifen use or with oophorectomy.

Experimental Methods

A historical cohort approach will be employed. 500 women with hereditary breast cancer, diagnosed since 1975, will be identified be identified by review of the pedigrees of families with BRCA1 or BRCA2 mutations. The medical charts of all of the breast cancer cases in the family, living and dead, will be reviewed. We will record the date of diagnosis, the type of surgical treatment performed (lumpectomy, unilateral mastectomy, or bilateral mastectomy), as well as the pathological stage and tumour grade, the use of adjuvant chemotherapy, radiotherapy, tamoxifen and oophorectomy.

We will compare the survival experiences of the women treated with the different surgical procedures, controlling for stage, nodal status, grade and the use of chemotherapy and radiotherapy. We will also evaluate additional survival benefits associated with oophorectomy and tamoxifen use in this cohort. The three principal endpoints will be local recurrence, contralateral breast cancer and death.

Progress To Date

As of June 1999, we have enrolled 310 study subjects in this study, including 213 women with BRCA1 mutations and 95 women with BRCA2 mutations. These women are obtained from 199 families with mutations, originating from seven clinical centers. Thus, study subject recruitment is more than 60% complete. We have completed the medical chart review of all of these patients and have been able to establish the year and place of diagnosis, the stage and grade of the tumour, the surgical treatment performed, and the use of ovarian ablation, chemotherapy or oophorectomy. We have not performed a complete survival analysis on this cohort yet because enrollment is ongoing. Nevertheless, the details of the 310 patients are presented in Tables 1 to 3.

Table 1. Description of Study Subjects

Total number of cases in study	310
Centre University of Toronto	69
Creighton	106
Pennsylvania	43
British Columbia	29
Chicago	19
Montreal	28
McGill	16
BRCA1	213
BRCA2	95
BRCA1/2	2
Mean age of diagnosis	41.7 years
Mean duration of follow-up	8.6 years

Table 2. Stage Distribution of 310 Tumours

		Number	Deceased (%)	mean age of dx	year of dx
Stage	I	139	18 (12.9)	42.3	1988.5
	II	171	32 (18.7)	41.1	1988.3
Size	< 2cm	157	22 (14.0)	42.3	1988.8
	> 2cm	153	28 (18.3)	41.0	1988.1
Age	<40	148	31 (20.9)	34.1	1988.0
	>40	162	19 (11.7)	48.5	1988.8
Nodal Status					
	negative	207	30 (14.5)	42.0	1988.4
	positive	101	20 (19.8)	40.9	1988.4
	missing	2			

Table 3. Treatment Distribution of 310 cases

	Number	Deceased (%)	mean age of dx	year of dx
Surgery:				
lumpectomy	109	23 (21.1)	41.8	1990.4
unilateral mastectomy	127	24 (18.9)	42.5	1986.0
bilateral mastectomy	74	3 (4.1)	40.1	1989.7
Radiotherapy				
yes	130	21 (16.2)	41.3	1990.0
no	174	23 (13.2)	41.8	1987.4
missing	6			
Chemotherapy				
yes	181	21 (11.6)	39.8	1990.0
no	122	22 (18.0)	44.1	1986.4
missing	7			
Tamoxifen				
yes	77	3 (3.9)	45.4	1990.9
no	216	35 (16.2)	40.3	1987.7
missing	17			
Bilateral Oophorectomy				
yes	110	10 (9.1)	42.8	1988.0
no	190	34 (17.9)	41.2	1988.7
missing	10			

Table 4. Multivariate risk ratios for selected factors associated with mortality at ten years among 283 patients with complete information.

Factor	Hazard Ratio	95% Confidence Limits
Surgical treatment		
Lumpectomy	1.00	
unilateral mastectomy	0.51	(0.20 – 1.29)
bilateral mastectomy	0.39	(0.11 – 1.42)
Age at diagnosis		
<40	1.00	
>40	0.30	(0.10 – 0.87)
Mutation		
BRCA1	1.00	
BRCA2	1.07	(0.38 – 3.05)
Tamoxifen		
never	1.00	
ever	0.28	(0.03 - 2.27)
Ovarian ablation		
no	1.00	
yes	0.59	(0.21 – 1.64)
Chemotherapy		
no	1.00	
yes	0.63	(0.26 – 1.52)

Table 5. Multivariate risk ratios for selected factors associated with contralateral breast cancer at ten years among 259 patients with no prophylactic mastectomy at time of initial diagnosis.

Factor	Hazard Ratio	95% Confidence Limits
Age at diagnosis		
<40	1.00	
>40	1.34	(0.73 – 2.47)
Mutation		
BRCA1	1.00	
BRCA2	0.71	(0.36 – 1.42)
Tamoxifen		
never	1.00	
ever	0.49	(0.19 – 1.23)
Ovarian ablation		
no	1.00	
yes	0.21	(0.07 – 0.59)
Chemotherapy		
no	1.00	
yes	1.02	(0.55 – 1.88)

Data Analysis

The data will be analyses by the Cox proportional hazards model using the SAS package. The 500 cases will form a historical cohort. Entry into the cohort will defined at the time of diagnosis of first breast cancer. The data will be analysis at the time the cohort of 500 women is assembled, and at periods of five and ten years thereafter. Patients will be followed until either death, loss to follow-up, or the date of data analysis.

A survival curve will be constructed for the overall cohort and for the following three subgroups: 1) women treated with mastectomy +/- radiotherapy; 2) women treated with unilateral mastectomy; 3) women treated with bilateral mastectomy. Patients may opt for further preventive surgeries following the initial treatment and may go from group 1) to group 2) or 3), or from group 2) to 3) during the time frame of this study. They will be treated in three ways: 1) they will remain in the initially assigned group; 2) they will be excluded from consideration; 3) they will be considered to change groups and will be analyzed as such using time-dependent covariates. The principal endpoint for the comparison of surgical groups will be death. The Cox regression analysis allows for the control of extraneous variables which are related to prognosis. To control for these prognostic factors, the following will be entered into the Cox model: tumour size (in cm); number of positive axillary nodes; age at diagnosis (years); menopausal status (pre, peri, post); ER status (+/-); PR status (+/-); use of radiotherapy (yes/no); use of adjuvant chemotherapy (yes/no); tamoxifen (yes/no, and duration of use in months); oophorectomy (yes/no). For those women who underwent oophorectomy more than one year after the treatment of the breast cancer, oophorectomy will be treated as a time-dependent covariate.

The analysis will be conducted separately for the BRCA1 and BRCA2 subgroups. It will also be possible to estimate the mortality hazard ratio for BRCA1 carriers compared with BRCA2 carriers.

The use of tamoxifen will be studied as an independent prognostic factor. In this tamoxifen substudy there will be two endpoints: contralateral breast cancer incidence and death. Again, the data will be analyzed separately for the BRCA1 and BRCA2 carriers. The usefulness of tamoxifen will be assessed in the cohort as a whole and separately in the three subgroups listed above. Similarly a history of oophorectomy will be studied as an independent risk factor in the overall cohort and in the subgroups defined above.

CONCLUSIONS

This preliminary data set confirms our ability to ascertain the relevant clinical data and outcomes on BRCA1/BRCA2 carriers. A crude univariate analysis of this data suggests that improved survival is associated with age of diagnosis over 40, small tumours, stage I tumours, bilateral mastectomy, oophorectomy, chemotherapy, and tamoxifen. However, this preliminary analysis has not been adjusted for covariates (age and other prognostic features) or for variable length of follow-up. These adjustments will be made on the final data set, using the methods

described in Data Analysis, above. It will also be necessary to estimate the prognostic factors separately for the subgroups of women with BRCA1 mutations and BRCA2 mutations.

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